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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/614,275	07/08/2003	Wei-Wu He	PF219D1	7739

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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 09/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/614,275	HE ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45 and 48-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-45 and 48-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *August 15, 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendments to the specification in the Reply of August 18, 2006 have been considered and entered.

2. Claims 12, 34 and 54 have been amended, new claims 63 and 64 added and Claims 46 and 47 were cancelled in the Reply of August 18, 2006. The amendment of Claims 12, 34 and 54 to recite that the DNA clone of ATCC deposit No. 209005 is a genomic clone instead of a cDNA clone, and new claims 63 and 64 as being drawn to the amino acids comprising the homeodomain of SEQ ID NO:2 has been considered and entered.

3. Claims 1-45 and 48-64 are all the pending claims for this application and all the claims under examination.

Election/Restrictions

4. Applicant's election with traverse of Group I (Claims 1-3, 6-25, 28-45 and 48-64) in the reply filed on August 18, 2006 is acknowledged. The traversal is on the ground(s) that the two inventive groups, which are restricted on the basis of SEQ ID NOS: 2 and 4, are not patenably distinct because the amino acid sequences differ by only one amino acid (i.e., the sequences are 99% identical (p. 10, ¶4); Exhibit A), and since Claims 45 and 56 of Group I encompass proteins at least 95% identical to SEQ ID NO:2, the search of Group I would then encompass the protein of SEQ ID NO:4.

In view of Applicants arguments and the evidentiary support provided in Exhibit A, the restriction has been withdrawn as between Groups I and II. Accordingly, Claims 1-45 and 48-64 are all the claims under examination.

Information Disclosure Statement

5. The copies of references A1-A85 submitted by Applicants or cited by the Examiner in parent application no., 09/105,470 (USPN 6,617,129), and the copies of references A86-A96 submitted with the IDS of August 15, 2006 for the instant application have been considered and entered.

Specification

6. The use of the trademarks, e.g., pCAT ™, BaculoGold™, rediprime™, CHROMA SPIN- 100™, ExpressHyb™, has been noted in this application. A trademark should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 1-45 and 48-64 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well established utility.

Claims 1-45 and 48-64 are drawn to proteins and compositions thereof comprising amino acid residues 1-234 or 2-234 of SEQ ID NO:2 or 4, or a full-length polypeptide with or without an N-terminal methionine residue encoded by the genomic DNA of ATCC accession no. 209005 or the cDNA of ATCC accession no. 209006, or polypeptides comprising at least 30 or 50 contiguous amino acid residues of SEQ ID NO:2 or 4, or polypeptides comprising at least 30 or 50 contiguous amino acid residues encoded by the genomic DNA of ATCC accession no. 209005 or the cDNA of ATCC accession no. 209006, or a human protein having at least 95% identity to amino acid residues 1-234 of SEQ ID NO:2, or a human protein having at least 95% identity to the full-length polypeptide encoded by the genomic DNA of ATCC accession no. 209005 or the cDNA of ATCC accession no. 209006, and heterologous proteins comprising immunoglobulin Fc domains, glycosylated proteins, PEG-fused proteins, expressing the protein from a cell for recovery for the foregoing proteins and polypeptides, and polypeptides comprising amino acid residues 122-188 or 124-183 of SEQ ID NO:2.

The specification discloses the isolation of a genomic clone, SEQ ID NO:8, and a cDNA clone, SEQ ID NO: 1 or 3, which encodes a protein, SEQ ID NO:2 or 4 which is disclosed as human NKX3.1 (see [0022, 0024]). The protein is disclosed to have significant homology to drosophila NK-3 gene (see [0026]). Based on the structural similarity between the homeodomain for the human NKX3.1 gene and drosophila and

mammalian NK-3-like genes, the specification asserts that the newly disclosed human NK-3 related prostate specific protein has the utility of a transcription factor regulating both prostate development, the androgen-driven maintenance of prostatic differentiation in adults and the opposing processes of androgen-driven differentiation of prostatic tissue and loss of that differentiation during the progression of prostate cancer (see [0008]).

The assertion that the disclosed protein has biological activities similar to known NK-3 related proteins is not credible in the absence of supporting evidence, because the relevant literature reports numerous examples of polypeptide families wherein individual members have distinct, and even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical conditions (p.

9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF-β family (1987, Cell 49:437-8, esp. p. 438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there

are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Bork (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. Finally, Bowie et al. (1990, Science 247:1306-1310) state that determination of three dimensional structure from primary amino acid sequence, and the subsequent inference of detailed aspects of function from structure is extremely complex and unlikely to be solved in the near future (p. 1306). Thus, the specification fails to support the asserted credible, specific and substantial utility of growth factor activity.

The specification does not support a credible, specific and substantial utility regarding the claimed polypeptides for purposes unrelated to the asserted biological activity. For example, the specification asserts that the expressed homoedomain portion of the human and murine NKX3.1 proteins (designated NKX3.1HD) each have comparable DNA binding specificity as NK-2 homeodomains in a gel mobility shift assay (Example 7). The specification does not disclose any correlation between the DNA binding activity and the role of the protein in transcriptional regulation of any gene. The

specification does not disclose a correlation between any specific disorder and an altered level or form of the claimed polypeptides. Also, the specification does not predict whether the claimed polypeptides would be overexpressed or underexpressed in a specific, diseased tissue compared to the healthy tissue control.

The instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a credible, specific and substantial utility. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed polypeptides. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-45 and 48-64 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Biological Deposit Requirements

9. Claims 12-22, 34-44 and 54-62 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (a) known and readily available to the public; (b) reproducible from the written description.

1) It is unclear if a genomic DNA or cDNA clone encoding a human NK-3 related prostate specific protein (SEQ ID NO:2 or 4) having the exact chemical identity of the HPFCA19 genomic clone (SEQ ID NO: 8) or the NKX3.1 cDNA clone (SEQ ID NO: 1 or 3) is known and publicly available, or can be reproducibly isolated without undue experimentation. The Examiner's search of the ATCC website for ATCC deposit nos. 209005 (HPFCA19 genomic clone) and 209006 (NKX3.1 cDNA clone) did not identify any submission of a deposit under these numbers. Further searching of the website using search terms nkx3.1, HPFCA19 and nk-3 related prostate specific gene 1, did not reveal any submissions bearing any resemblance to this gene (see attached copy of search output).

2) It is noted that Applicant's specification discloses deposits having been made with the ATCC on April 28, 1997 for each of the clones designated 209005 and 209006 [0009, 0022]. If the clones were assigned a different accession number by the ATCC than disclosed in the specification and claims, Applicant's are requested to provide a verified statement and that amendments to the claims and specification are made as appropriate. Thus Applicant's referral to the deposits of the DNA clones is an insufficient assurance that the required deposit has been made and all the conditions of 37 CFR 1.801-1.809 have been met. Without a publicly available deposit of the above DNA clones, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (a) the claimed full-length NKX3.1 polypeptide; (b) a genomic DNA clone (HPFCA19) and a cDNA clone (NKX3.1) encoding the NKX3.1 polypeptide; and/or (c) cloning vectors encoding the nucleic acid sequence(s) for a full-length NKX3.1 protein is an unpredictable event. Deposit of the genomic DNA clone and/or a cDNA clone for each of HPFCA19 and NKX3.1, respectively, would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

If the deposit for the genomic DNA clone and a cDNA clone encoding the NKX3.1 polypeptide is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions

upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete

name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

Written Description Requirements

10. Claims 23-45 and 48-62 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polypeptides comprising contiguous regions of 30 or 50 amino acid residues of SEQ ID NO:2 or 4 or from a full-length protein encoded by DNA of ATCC deposit No. 209005 or 209006, or having at least 95% sequence identity to amino acid residues 1-234 of SEQ ID NO:2 or from a full-length protein encoded by

DNA of ATCC deposit No. 209005 or 209006. The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polynucleotides, and therefore conception is not achieved until

reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the sequence set forth in SEQ ID NO:2 or 4 or amino acid residues 122-188 or 124-183 of SEQ ID NO:2 (homeodomain region), but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Enablement Requirements

11. Claims 1-45 and 48-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making a peptide comprising the homeodomain of the NKX3.1 protein (amino acid residues 122-188 or 124-183 of SEQ ID NO:2 (Claims 63 and 64)), does not reasonably provide enablement for making or using a full-length human (or murine) NKX3.1 protein of SEQ ID NO:2 or 4 or a full

length NKX3.1 protein encoded by genomic DNA or cDNA of ATCC Deposit No.209005 and 209006 or proteins having at least 95 % identity with the protein of SEQ ID NO:2 or 4 or peptides comprising 30 or 50 contingous amino acids of SEQ ID NO:2 or 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

The interpretation of Claims 1-45 and 48-64 is discussed supra. There is no functional limitation in the claims as far as the polypeptide.

The specification teaches that the human NKX3.1 gene (human NK-3 like prostate specific protein) most closely resembles drosophila NK-3 gene (47/60 aa identity within the homeodomain) [0026], general methods for expressing recombinant proteins from NKX3.1 encoding genomic clones and cDNAs using expression vectors and host cells [0051-0065], modified forms of the proteins comprising Fc fusion molecules [0066], fragments and derivatives of the polypeptides [0068-0076], polypeptides being at least 95% identical to the original proteins encoded by the

NKX3.1 DNA clones [0077, 0079], N-terminal deletions of NKX3.1 proteins [0087-0088], and prophetic examples for expression of the full-length NKX3.1 protein by E. coli (Example 1), baculovirus (Example 2) and mammalian cells (Examples 3 and 4).

A. The specification is not enabling for expressing a recombinant full length NKX3.1 protein from a host cell

The only working example showing actual expression of any part of a NKX3.1 protein is in Example 7, where Applicants demonstrate E. coli expression of the putative homeodomain portion of the human and murine protein (PCR-selected cloning of the domain) and binding of selected DNA fragments in an experiment allegedly correlating structure and function. Applicant's own admission is "given its high content of proline and arginine residues (which are inefficiently translated in E. coli), it was predicted that the full length murine NKX3.1 **would be poorly expressed in bacterial cells** (Abate, C. et al., Mol. Cell. Biol. 11:3624-3632 (1991)). Therefore, the region containing the murine and human homeodomain (NKX3.1HD) was expressed as a hexahistidine fusion polypeptide in E. coli, and a highly purified protein was obtained by nickel affinity chromatography" [0208].

The specification does not provide any working examples of: 1) a fully expressed protein much less any fragments, variants or derivatives thereof having any biological activity (e.g., transcriptional regulation), 2) proteins and polypeptides, fragments, variants and derivatives thereof being at least 95% identical to the wild type protein and retaining biological activity, and 3) the putative homeodomain providing any functional signal or activity (e.g., transcriptional regulation) upon binding to a synthetic DNA

peptide in vitro, and moreover, specifically teaches away from being able to even express a full-length NKX3.1 protein in a bacterium. Thus in view of the prior art and Applicant's admissions of record, the specification is strongly dispositive to one of ordinary skill in the art being enabled for making the NKX3.1 protein and its fragments, variants and derivatives thereof.

b) The specification is not enabling for showing a correlation between NKX3.1 mRNA and protein expression in vitro or in vivo

All of the claims are directed to an isolated NKX3.1 protein or polypeptide without the specification even so much as demonstrating an expressed full-length recombinant protein, an isolated or purified protein from a natural source or that a functional, translational product for the human NKX3.1 protein can be obtained from a NKX3.1 mRNA. Examples 4, 5 and 8-10 of the specification all demonstrate NKX3.1 mRNA expression in various tissues under varying conditions without showing correlative protein expression levels. Those of skill in the art, recognize that expression of mRNA, specific for a tissue type, does not necessarily correlate nor predict equivalent levels of polypeptide expression. There are many steps in the pathway leading from DNA to protein, and all of them can in principle be regulated. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) illustrate post-transcriptional regulation of ferritin wherein the translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferin receptor polypeptide is translated.

For example, the textbook Genes VI (1997) by Benjamin Lewin points out that control of gene expression can occur at multiple stages and that production of RNA cannot inevitably be equated with the production of protein. More recently, Greenbaum *et al.* (Genome Biology, 2003, Vol. 4, Issue 9, pages 117.1-117.8) cautions against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page 2nd column) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved

in protein synthesis and degradation have to be better understood. Hence, due to the teachings above, it would appear that production of mRNA, as a general rule, would not inevitably be predictive of equivalent levels of protein.

c) The specification is not enabling for making or using human proteins and polypeptides having at least 95% identity with the full length human polypeptide for NKX3.1, or for using fragments and derivatives of the human NKX3.1 polypeptide

Claims 23-44 are directed to protein fragments of SEQ ID NOS: 2 or 4, Claims 45 and 48-61 are directed to a human variants having at least 95% identity with the human NKX3.1 protein, and Claims 63 and 64 are directed to a fragment of the human NKX3.1 protein comprising the putative homeodomain. The claims encompass an unreasonable number of inoperative polypeptides, which the skilled artisan would not know how to make or use. While specification suggests that NKX3.1 protein of SEQ ID NO: 2 or 4 is homologous to the drosophila NK-3 gene and other human NK-3 like genes, what related function it possesses is undisclosed. Knowledge of one NK-3 prostate related protein and its function does not provide predictability about function of a structurally related protein, even within the same class.

In the absence of any showing of a function or biological activity for the wild type, full-length human (or murine) NKX3.1 protein, the specification is not any more revealing of human NKX3.1 protein fragments or derivatives much less that for human homologues having any function or practical use. The skilled artisan would not know how to use non-identical polypeptides on the basis of teachings in the prior art or specification. Even if the claimed polypeptides had a function, the specification does not

provide guidance using polypeptides related to (i.e., at least 95% identity) but not identical to SEQ ID NO:2 or 4. The claims are broad because they do not require the claimed polypeptide to be identical to the disclosed sequence and because the claims have no functional limitation.

Furthermore, the claims are not commensurate in scope with the enablement provided in the specification. The specification does not support the broad scope of the claims which encompass all modifications to the amino acid sequence because the specification does not disclose the following:

The general tolerance to modification and extent of such tolerance;

The specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical; and

The specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in manner reasonable correlated with the scope of the claims broadly including any number of additions, deletions, or substitutions. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

Without such guidance, the changes which can be made in the protein's structure and still maintain biological activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc.

v. Chugai Pharmaceutical Co. Ltd., 927 F,2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).f

Further protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252).

Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975).

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

In view of the lack of guidance, lack of examples and lack of predictability associated with regard to producing and using the myriad proteins, polypeptides, and

variants and derivatives thereof encompassed by the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. As discussed under section 11, supra, Claim 64 is enabled for making (expressing) an amino acid sequence comprising amino acid residues 124-183 of SEQ ID NO:2, and the claim is not limited by function.

13. Claim 64 is rejected under 35 U.S.C. 102(a) as being anticipated by Sciavolino et al. (Developmental Dynamics 209:127-138 (May 1997); hereinafter referred to as "Sciavolino").

The interpretation of Claim 64 is discussed supra.

Sciavolino discloses a murine NKX3.1 homeodomain comprising having 100% identity with amino acid residues 124-183 of SEQ ID NO:2 of Claim 64 (see attached copy of sequence alignment (1 page); MPEP 719.05 "these searches are stored in SCORE (The Supplemental Complex Repository for Examiners), which is part of the

permanent file wrapper and satisfies all National Archives Electronic Records Management requirements"). Sciavolino discloses "given its high content of proline and arginine residues (which are inefficiently translated in E. coli), we predicted that the full length murine NKX3.1 **would be poorly expressed in bacterial cells**." The region containing the murine and human homeodomain (NKX3.1HD) was expressed as a hexahistidine fusion polypeptide in E. coli, and a highly purified protein was obtained by nickel affinity chromatography. (p. 130, Col. 1, ¶2 to Col. 2, ¶1).

Applicants are reminded that since the claim recites "comprising" language, peptide sequences such as NK-3 related homoedomains with sequence homology to the inventive homedomain region, are encompassed by and therefore anticipated by Sciavolino.

14. Claim 64 is rejected under 35 U.S.C. 102(b) as being anticipated by Bieberich et al. (J. Biol. Chem. 271:31779-31782 (December 13, 1996); hereinafter referred to as "Bieberich").

The interpretation of Claim 64 is discussed supra.

Birberich discloses a murine NKX3.1 homeodomain comprising having 100% identity with amino acid residues 124-183 of SEQ ID NO:2 of Claim 64 (see attached copy of sequence alignment (1 page); MPEP 719.05 "these searches are stored in SCORE (The Supplemental Complex Repository for Examiners), which is part of the permanent file wrapper and satisfies all National Archives Electronic Records

Management requirements"). Bieberich discloses comparison of NKX3.1 homeodomain amino acid sequence with other NK-related homeodomains (Fig. 1).

Applicants are reminded that since the claim recites "comprising" language, peptide sequences such as NK-3 related homoedomains with sequence homology to the inventive homeodomain region, are encompassed by and therefore anticipated by Birberich.

Conclusion

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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